



**Mosquito
Management**



Field trials

at a glance



Fludora® Fusion Trial results

Fludora® Fusion has been assessed as part of an extensive trial program across more than a dozen countries in Africa and Asia.

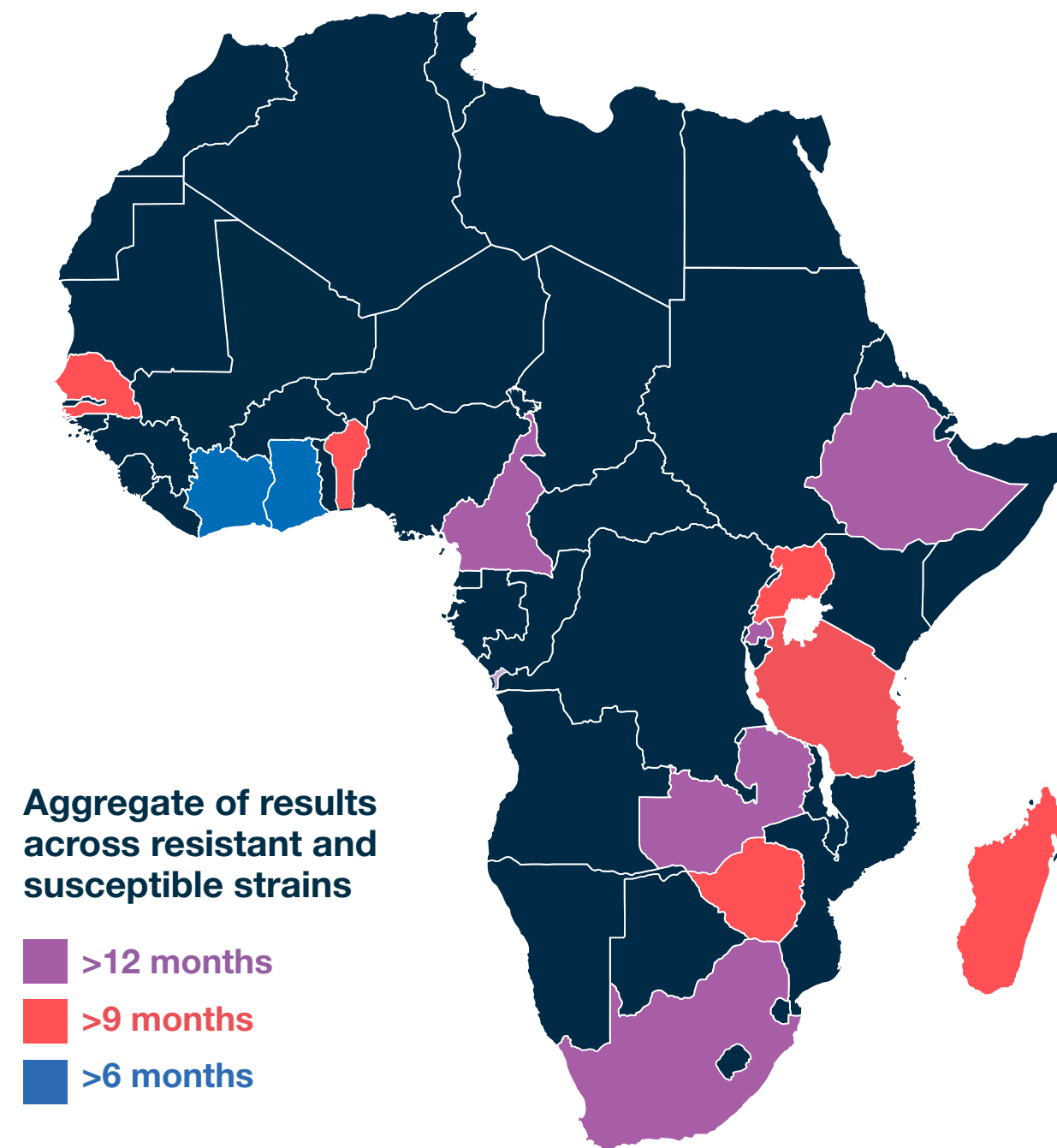
Knowing that variability of results can be a challenge in IRS operations, we used a broad range of settings to confirm that the combination generally gives more robust results than either active ingredient applied alone. In doing so, we were able to take into account the influence of different spray operators, spray equipment, surface types, and climatic settings. This gives greater confidence in Fludora® Fusion over similar products which have minimal field testing completed.

The results of these trials are summarized on the following pages. We would like to emphasize that the experience of one trial location should not be seen as predictive for the results across an entire country. The extensive results generated across multiple countries gives confidence that Fludora® Fusion is a robustly performing product across most situations and conditions. Please note that most of these assessments reflect cone-bioassay results with mortality measured at 72-hours post exposure (unless otherwise stated).

Table of Content

- Fludora® Fusion – Trials results 3
- Relevance of Deltamethrin inclusion in Fludora® Fusion 4
- Summary of LECA Study:
The potential for neonicotinoid-pyrethroid combinations in insecticide-resistance management 5

Summary of Residual Activity observed from trials



Countries included:

Benin, Ethiopia, Ghana, Madagascar, Rwanda, Senegal, South Africa, Tanzania, Zimbabwe, Zambia, Côte d'Ivoire, Cameroon

Trial results pending:

Mali

Country	Trial Duration	Trial Type	Best Results	Mosquitoes Tested / Susceptibility status
 Benin Feedback from Principal Investigator "Fludora® Fusion showed very good and lasting efficacy for IRS against resistant Anopheles." "The residual effect of Fludora® Fusion evaluated over 10 months is a good news for IRS interventions."	11 Months	Village Hut	10 months residuality on cement Faster knockdown than reference products	Mosquitoes Tested: <i>An. gambiae</i> Susceptibility status: Susceptible and resistant to pyrethroids
 Ghana Feedback from Principal Investigator "Fludora® Fusion (a combination of Clothianidin and deltamethrin) performed better than other insecticides included in this study, including against the individual insecticide components applied alone."	12 Months	Phase II Experimental Huts	9 months protection on cement	Mosquitoes Tested: <i>An. gambiae s.l.</i> Susceptibility status: Multi-resistant
 Ivory Coast Feedback from Principal Investigator "Fludora® Fusion induced significantly greater mortality than the single active ingredients alone." "Significantly reduced blood feeding."	9 Months	Experimental Huts	7.8 months protection	Mosquitoes Tested: Free Flying <i>An. gambiae s.l.</i> - Multi-Class resistant <i>An. gambiae s.s.</i> (Kisumu) - Susceptible
 Ethiopia Feedback from Principal Investigator "The residual activity of Fludora® Fusion outperformed [the reference products]." "Fludora® Fusion can be considered as an alternative insecticide for the control of Anopheles arabiensis in Ethiopia."	12 Months	Phase II Experimental Huts	Efficacious above 80% threshold for 12 months	Mosquitoes Tested: <i>An. Arabiensis</i> (DebreZeit strain) Susceptibility status: Susceptible
 Madagascar Feedback from Principal Investigator "IRS with Fludora® Fusion shows potential to improve and prolong the control of malaria transmission in Madagascar." "Due to its two different modes of action, Fludora® Fusion can be deployed to complement pyrethroid LLINs in pyrethroid resistant areas."	9 Months	Experimental Huts	6 months protection across all surfaces types	Mosquitoes Tested: Wild vectors - DDT resistance in some species Susceptible <i>An. Arabiensis</i> Lab Strain Susceptibility status: Susceptible
 Cameroon Feedback from Principal Investigator "Fludora® Fusion could help to significantly reduce transmission of malaria by pyrethroid-resistant mosquito vectors." "Altogether, this study shows that Fludora® Fusion is an important addition to the current portfolio of IRS insecticides."	12 Months	Experimental Huts	12 months residuality at 90-100% protection against Kisumu Induced high mortality against wild <u>Free Flying</u> pyrethroid resistant <i>An. funestus</i> Efficient against CYP6P9a -based and GST -based resistant mosquitoes	Mosquitoes Tested: <i>An. funestus s.s.</i> (resistant) <i>An. gambiae s.l.</i> (resistant)
 Tanzania Feedback from Principal Investigator "Its durability on mud, concrete and thatch surfaces...and its efficacy against pyrethroid-resistant mosquitoes should help to promote its widespread use in Sub-Saharan Africa for IRS."	9 Months	Phase II Experimental Huts	Fludora® Fusion induced ≥ 80 % mortality for over 12 months (48 hours)	Mosquitoes Tested: <i>An. arabiensis</i> (Wild) (Pyrethroid resistant) <i>An. gambiae</i> (Kisumu strain) (Susceptible) <i>An. gambiae</i> (Muleba-Kis strain) (Pyrethroid resistant)
 Tanzania Feedback from Principal Investigator "The impact of Fludora® Fusion on mortality...remains significantly high for up to 340 days. It implies single spraying cycle...and consequently less expenditure on insecticide procurement per year."	12 Months	Experimental Huts	Fludora® Fusion induced ≥ 80 % mortality for over 12 months (48 hours)	Mosquitoes Tested: <i>An. arabiensis s.s.</i> (Locally Colonised) Susceptibility status: Multi-resistances to pyrethroids
 Rwanda Feedback from Principal Investigator "Fludora® Fusion showed a good knockdown effect on both surfaces." "A worthy vector control tool for insecticide resistance management."	9 Months	Experimental Huts	100% Mortality at 24 hrs across all 12 months on cement surfaces 12 months protection on cement and mud	Mosquitoes Tested: <i>An. gambiae</i> (Strain: Kisumu) Susceptibility status: Susceptible
 South Africa Feedback from Principal Investigator "These data indicate Fludora® Fusion is suited for integration with the IRS programme of the National Malaria Control Programme of South Africa."	12 Months	Village Hut	12 Month 100% mortality (Matching DDT) on: Mud, cement and painted	Mosquitoes Tested: <i>An. arabiensis</i> (KGB) Susceptibility status: Fully Susceptible
 Senegal Feedback from Principal Investigator "Fludora® Fusion may be recommended for use in IRS for malaria control and particularly in areas of vectors resistance to one or more insecticide families."	11 Months	Village Bedrooms Experimental Huts	At least 10 months protection on cement	Mosquitoes Tested: <i>An. coluzzii</i> - DDT susceptible <i>An. arabiensis</i> (laboratory strain) - Multi-resistance
 Zimbabwe Feedback from Principal Investigator "Fludora® Fusion showed higher residual effect than [the reference Product] for both mosquito species on brick, cement and mud surfaces." "Fludora® Fusion is recommended for use as part of an integrated resistance management programme."	12 Months	Village Hut	Residuality against Wild Strain: Brick: 11 months (48 hours) Cement: 12 months (48 hours) Mud: 12 months (72 hours)	Mosquitoes Tested: <i>An. arabiensis</i> (Strain: KGB) <i>An. gambiae s.l.</i> (Wild) Susceptibility status: Both susceptible
 Zambia Feedback from Principal Investigator "Throughout the evaluation period, the efficacy and residual activity of Fludora® Fusion was far superior compared to the benchmarking product..."	12 Months	Village Hut	Cement: 12 months residuality at 24 hours Mud: 8 months residuality at 48 hours 12 months post 48 hours	Mosquitoes Tested: <i>An. gambiae</i> (Kisumu) Susceptibility status: Susceptible



Relevance of Deltamethrin inclusion in Fludora® Fusion

In a context of high levels of pyrethroid resistance, the rationale for combining a novel mode of action with a pyrethroid may not be immediately apparent. These two active ingredients have unrelated modes of action, which is important in itself, but the way in which these two active ingredients interact and work in conjunction with each other to achieve an effect greater than the sum of its parts adds even more validity to the approach.

The binding of Clothianidin molecules to the nicotinic acetylcholine receptors (nAChR) ultimately has the effect of causing sodium channels to open, triggering action potentials in the nerve cells. As an action potential propagates along the nerve cell, the sodium channels are sequentially opened. The open sodium channels are targets for the second active ingredient, Deltamethrin, which acts by preventing the open sodium channels from closing. The nerve is therefore unable to re-establish the potential difference across the nerve cell membrane which is a prerequisite for any future action potentials (nerve signals).

This complementary effect of the two active ingredients working together as described, results in overall more rapid knock-down and death than the effect of Clothianidin alone. So even where there is pyrethroid resistance, not only is there the fundamental effect of clothianidin but deltamethrin activity is enhanced as well.

There has been some talk about the excito-repellent effect of deltamethrin in the Fludora® Fusion combination and its impact on the ability of mosquitoes to stay on surfaces long enough to pick up a lethal dose. This theory has not been well supported by our various field studies carried out with free-flying mosquitoes in the field. Very commonly in such trials, higher free-flying mortality from the Fludora® Fusion treatment arms was observed than with the clothianidin solo active ingredient. This is largely due to significance of the complementary effect of the two unrelated modes of action.

As the two active ingredients have totally different modes of action, exerted at the same time and not sequentially, this makes simultaneous development of resistance mechanisms to both of them harder and unlikely. Simply put, combining a novel mode of action with a second mode of action, slows down the likelihood of resistance development to the novel mode of action. Fludora® Fusion therefore protects itself so it can continue to protect people.

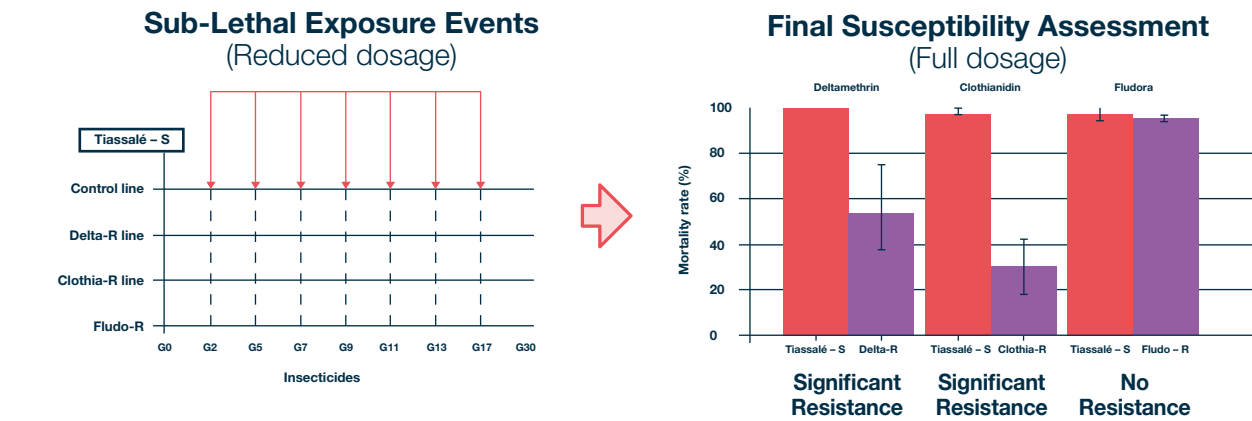
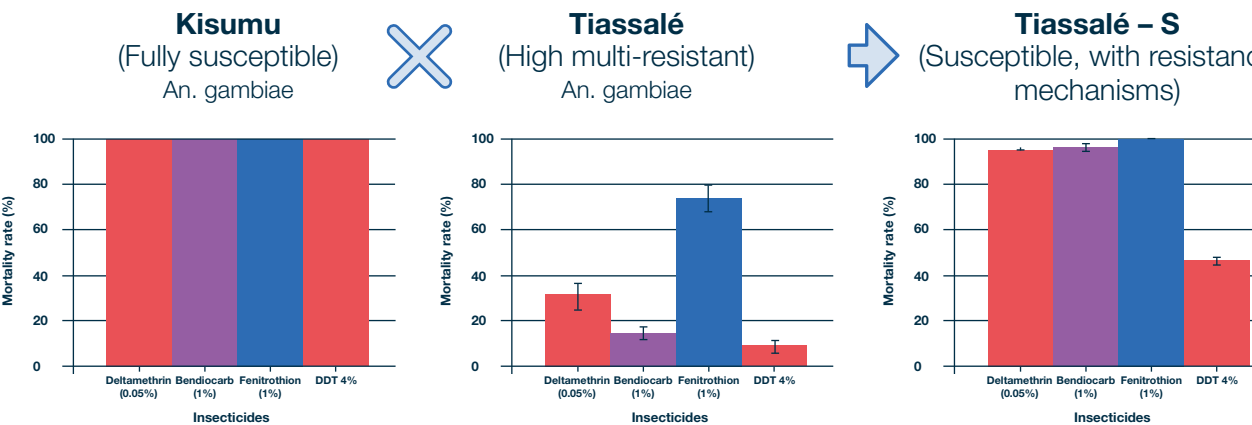
Summary of Laboratoire d'Ecologie Alpine (LECA) Study: Neonicotinoid-pyrethroid combination's potential for insecticide resistance management illuminated

As Clothianidin is a novel mode of action to the vector control arena, and Fludora® Fusion was the first dual active ingredient product designed specifically for IRS, the responsible action would be to study what can likely be expected in the future to better understand and guide best use of the product and insecticide class.

By crossing the fully susceptible Kisumu *Anopheles gambiae* s.s. strain with the highly multi-resistant strain Tiassalé, resistance mechanisms were introduced into the population, starting to reduce the susceptibility levels. This new strain was designated Tiassalé – S, a susceptible strain with resistance mechanisms.

Dividing the strain into four cohort lines, they were subjected to sequential sub-lethal exposure events to their respective active ingredients for 33 generations. This is representative of approximately 2 years of inappropriate dosing of the different insecticide products without rotation. When finally exposed to their full respective doses, to assess their susceptibility levels, it was found that significant resistance had developed to in both of the solo-active ingredient products, but resistance had not developed to Fludora® Fusion.

This is a clear proof of the concept that is harder and less likely to develop resistance to the active ingredients when exposed to more than one unrelated mode of action at the same time. As such, the product Fludora® Fusion protects itself and the integrity of Clothianidin, allowing for continued protection of people.



For further information: Zoh, M.G., Bonneville, JM., Tutagata, J. et al. Experimental evolution supports the potential of neonicotinoid-pyrethroid combination for managing insecticide resistance in malaria vectors. *Sci Rep* 11, 19501 (2021)

Overall conclusions from all trials:



These trials support a residual lifespan commonly in the range of 9 - 12 month. Where there are problematic surface types, then more limited residuality may be seen (less than 6 months). Even in these conditions, Fludora® Fusion performs as well as or better than alternatives.



The Fludora® Fusion combination can be expected to outperform the individual active ingredients applied solo at the same dose rates.



In experimental hut trials involving free-flying mosquitoes, no clear conclusion can be drawn regarding higher detergency or induced exiting attributed to the potential effects of deltamethrin in the mixture. Higher exiting does not indicate lower mortality. Fludora® Fusion more frequently achieved higher mortality levels of free-flying mosquitoes compared to either active ingredient applied alone.



Based on extensive testing and now operational experience, Fludora® Fusion is proven to be an effective and long-lasting IRS insecticide.

Feedback from Operational Use:

We surveyed representatives from six African countries that had used Fludora® Fusion in their malaria control programs. Here is what they have to say:

100% of respondents stated that Fludora® Fusion didn't create any additional logistics and transport challenges. The majority of respondents (86%) said that Fludora® Fusion was better than other insecticides they had used before, in terms of ease of logistics.

88% of respondents stated that Fludora® Fusion was better (ie. easier) than other insecticides in terms of mixing and spraying.

100% of respondents said that the acceptance of Fludora® Fusion by residents of sprayed houses was very high - higher than other insecticides used (mainly due to it being odourless and non-staining).





Find out more about Envu Against Malaria at:



Website



Data & Information Hub



Twitter



LinkedIn



E-Learning



The Address, 7th Floor, Workstyle Offices, Muthangari Drive, Westlands, Nairobi, Kenya.

Envu and the Envu logo are trademarks owned by Environmental Science U.S. LLC. or one of its affiliates.
©2023 Environmental Science U.S. LLC.

2023_0003 VerA Final